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(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Preparation of Derivatives of 6-Trifluoromethyl-1,3,5-Triazine

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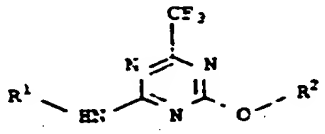
(30) (DE) P 41 39 624.3 1991/11/30

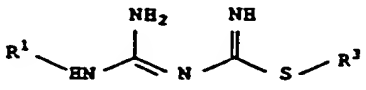
(57) 3 Claims

Abstract of the Disclosure: 6-Trifluoromethyl-1,3,5-triazines I



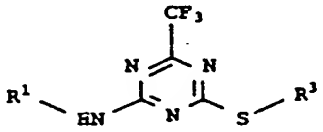
I

where R^1 is H and R^1 and R^2 are each a C-organic radical, are prepared by reacting a salt of an N-amidino-S-alkyl-isothiourea II



II

where R^3 is a C-organic radical of 1 to 10 carbon atoms, with a trifluoroacetic acid derivative III and a strong base IV to give a 6-trifluoromethyl-1,3,5-triazine V



V

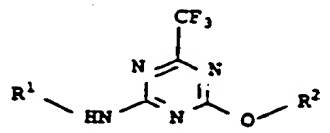
and reacting the product V in the presence of a base with an alcohol VII

$$R^2\text{-OH} \qquad \text{VII.}$$

The triazines I are useful intermediates for crop protection agents.

Preparation of derivatives of 6-trifluoromethyl-1,3,5-triazine

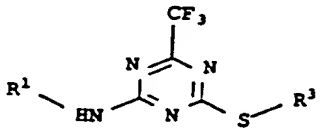
The present invention relates to a novel process for the preparation of derivatives of 6-trifluoromethyl-1,3,5-triazine of the general formula I



I

where R^1 is hydrogen or a C-organic radical and R^2 is a C-organic radical.

The present invention furthermore relates to a novel process for the preparation of derivatives of 6-trifluoromethyl-1,3,5-triazine of the general formula V



V

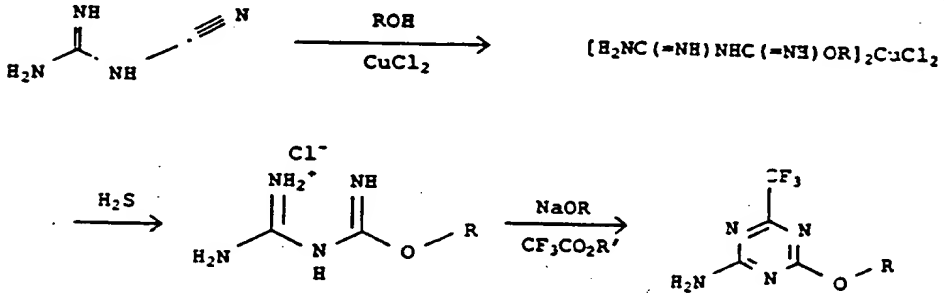
where R^1 is hydrogen or a C-organic radical and R^3 is a C-organic radical of 1 to 10 carbon atoms, which are used as intermediates for the preparation of I.

DE-A 16 70 147 relates to the reaction of N-amidino-S-alkylisothiuronium salts with carboxylic acid acyl equivalents to give 1,3,5-triazines. However, the high yields of 80-100% achieved thereby are obtained only in cyclization reactions with aromatic, nonpolar carbonyl chlorides. The synthesis of 2-amino-4-methylthio-6-trichloromethyl-1,3,5-triazine from the aliphatic, polar trichloroacetyl chloride and N-amidino-S-methylisothiourea, on the other hand, takes place in the presence of triethylamine with a yield of only 60%.

6-Trichloromethyl-substituted 1,3,5-triazines which carry amino in the 2-position and a thio

substituent in the 4-position are furthermore obtainable according to JP-A 48038715 in a two-stage reaction. Here, 2-methylthio-4,6-bis-(trichloromethyl)-1,3,5-triazine is first prepared and is then reacted with a corresponding amine with liberation of chloroform to give the end product.

2-Alkoxy-4-amino-6-trifluoromethyl-1,3,5-triazines are obtainable by a process disclosed in Yakugaku Zasshi 95 (1975), 499. Here, N-cyanoguanidine is converted into a bis-(N-amidino-O-alkylisourea)-copper chelate complex, from which the ligand is liberated by treatment with hydrogen sulfide and is then cyclized with a trifluoroacetate to give the end product.



R, R' = Organic radicals

Stoichiometric amounts of Cu salts are required for this process; in the absence of Cu salts, mainly guanylurea is formed instead of the N-amidino-O-alkyl-isourea (Kyushu Kogyo Daigaku Kenkyu Hokoku No. 12 (1962), 69-78).

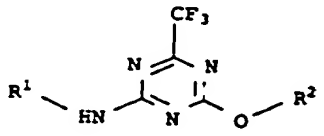
A major disadvantage of this process is that large amounts of copper salts have to be separated off as byproducts and disposed of, making a procedure on an industrial scale appear unprofitable.

Zh. Obshch. Khim. 37 (1967), 2247-2251 describes nucleophilic substitution in 1,3,5-triazines, where an electronegative substituent can be substituted by a less

electronegative one. However, no information is given concerning the behavior of 6-trifluoromethyl-1,3,5-triazines.

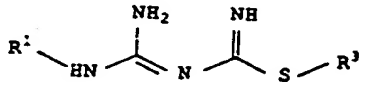
It is an object of the present invention to provide derivatives of 6-trifluoromethyl-1,3,5-triazine in a more advantageous manner.

We have found that this object is achieved by a process for the preparation of derivatives of 6-trifluoromethyl-1,3,5-triazine of the general formula I



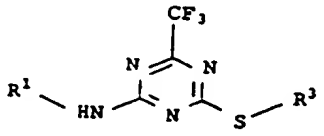
I

where R^1 is hydrogen or a C-organic radical and R^2 is a C-organic radical, wherein a salt of an N-amidino-S-alkyl-isothiourea of the general formula II



II

where R^3 is a C-organic radical of 1 to 10 carbon atoms, is reacted with a halide, ester or anhydride of trifluoroacetic acid (compound III) and with a strong base (IV) to give a derivative of 6-trifluoromethyl-1,3,5-triazine of the general formula V



V

and the latter is converted in the presence of a base (VI) with an alcohol of the general formula VII

$$R^2\text{-OH} \qquad \text{VII}$$

into the compound I.

The salts of the N-amidino-S-alkylisothioureas II which are used as starting materials are known (Chem. Ber. 100 (1967), 1874) or can be prepared from known substances with the aid of the processes described there.

Salts of the N-amidino-S-alkylisothioureas are understood as meaning the reaction products of the compounds II with acids. The type of acid is unimportant for the novel process since the compounds II are liberated from their salts with the aid of a base in the course of the reaction. The compounds II or their salts are advantageously prepared or stored as adducts of N-methyl-2-pyrrolidone.

On the basis of observations to date, the success of the novel process is not evidently dependent on the nature of the substituents R^1, R^2 and R^3.

In view of the use of the compounds I as intermediates for the synthesis of active ingredients, R^1 preferably has the following meanings:
hydrogen;
aliphatic radicals of 1 to 6 carbon atoms, such as C_1-C_6-alkyl, including in particular methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl or tert-butyl, or cycloalkyl having up to 7 carbon atoms, such as cyclopropyl, cyclopentyl or cyclohexyl;
aromatic radicals, such as phenyl.

R^2 and R^3 preferably have the following meanings:
C_1-C_4-alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl or tert-butyl;
C_3- or C_4-alkenyl, such as prop-2-en-1-yl, 1-methylprop-2-en-1-yl, but-2-en-1-yl or but-3-en-1-yl;
C_3- or C_4-alkynyl, such as prop-2-yn-1-yl or but-2-yn-1-yl;
C_3-C_6-cycloalkyl, such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, preferably cyclopentyl or cyclohexyl.

R^3 is preferably one of the radicals stated for R^2 or in particular benzyl which is unsubstituted or

substituted in the nucleus by methyl, chlorine, bromine or methoxy.

The stated radicals R^1, R^2 and R^3 may also carry substituents which are inert under the reaction conditions.

Suitable compounds III are mainly trifluoroacetic anhydride, halides of trifluoroacetic acid and the esters of trifluoroacetic acid, the methyl and the ethyl esters being very particularly preferred.

For the preparation of the 4-thioalkyl-6-trifluoromethyl-1,3,5-triazines V from II and III, it is advisable to use at least an equimolar amount of compound III; amounts of from 100 to 500, in particular from 100 to 250, mol %, based on II, of trifluoroacetic acid derivative III are preferred, unless III is also used as a solvent.

Suitable bases IV are inorganic and organic bases. The strength of the base used should be sufficiently great to enable it to liberate the N-amidino-S-alkylisothiourea II from its salt.

Preferred inorganic bases are alkali metal and alkaline earth metal hydroxides, and preferred organic bases are amines and alkali metal alcoholates.

The amount of base is usually from 110 to 300 mol % of the amount of the salt of N-amidino-S-alkylisothiourea II used. Larger amounts are possible but as a rule have no further advantages. In carrying out the reaction with a trifluoroacetate, 2-3 equivalents, based on the salt of II, of base are particularly preferred.

Advantageously, the salt of II and the compound III are initially taken and the base is metered in.

An inert solvent or diluent is preferably used in the reaction of II with III.

Examples of suitable solvents are aliphatic or aromatic hydrocarbons, which may also be substituted by halogen or nitro, cyclic or open-chain ethers, aliphatic alcohols or lower aliphatic ketones. Acid derivatives of

lower carboxylic acids, such as acetates, formamides or nitriles, are also suitable solvents.

If the reaction of II is carried out with trifluoroacetic anhydride or trifluoroacetyl chloride, ethyl acetate, diethyl ether and tert-butyl methyl ether are particularly preferred solvents.

When the reaction is carried out with a trifluoroacetate, methanol, tetrahydrofuran, tert-butyl methyl ether or the trifluoroacetate itself is particularly preferably used as the solvent.

The amount of solvent is not critical. Usually, the solvent is used in an amount which is from 1 to 5 times the amount of the N-amidino-S-alkylisothiourea II.

Particular conditions with regard to the pressure are not required and the reaction is generally carried out at atmospheric pressure.

The reaction is advantageously effected at from -40°C to the boiling point of the solvent, preferably from -20°C to 120°C, in particular from -10°C to 100°C.

It may be carried out either continuously or batchwise. In the continuous procedure, the reactants are preferably passed through a tube reactor.

The reaction mixture is generally worked up by removing the low boiling components under reduced pressure, neutralizing acid radicals and dissolving away the inorganic components while stirring the crude product with water.

The substitution of the thioalkyl group of the 6-trifluoromethyl-1,3,5-triazine V by an alkoxy group is advantageously carried out in an excess of the alcohol VII.

Suitable bases VI are inorganic and organic bases. Preferred inorganic bases are hydroxides and carbonates of alkali metal, alkaline earth metal or aluminum ions, and preferred organic bases are amines and alkali metal alcoholates.

The alkali metal alcoholates of the particular

alcohol VII are particularly preferably used.

The amount of base VI is in general from 1 to 200 mol %, based on the amount of 6-trifluoromethyl-1,3,5-triazine V. From 50 to 150 mol % of base are preferably used in the case of C_1- and C_2-alcohols VII, and over 50 mol % in the case of compounds VII having 3 or more carbon atoms.

The amount of solvent is not critical. Usually, the solvent is used in an amount which is from 5 to 10 times that of 6-trifluoromethyl-1,3,5-triazine V, an excess of alcohol VII preferably being used as a solvent.

For complete conversion, the amount of alcohol of the formula VII must be at least equimolar relative to the amount of 6-trifluoromethyl-1,3,5-triazine V used. If no additional solvents are used, from 4 to 5 mol of the alcohol V per mol of 6-trifluoromethyl-1,3,5-triazine V are preferably employed.

The reaction of V with VII is carried out, as a rule, at from -40°C to the boiling point of the particular solvent, preferably from -30°C to 150°C, in particular from -10 to 80°C, particularly preferably from 0 to 50°C.

The reaction mixture is worked up in a conventional manner, as a rule by removing the low boiling components under reduced pressure after neutralization.

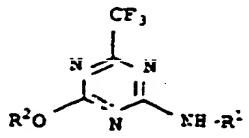
The reaction of V with VII can be carried out both continuously and batchwise. In the continuous procedure, the reactants are passed, for example, over a fixed bed of an insoluble base, or the reaction is carried out in a solution saturaced with the product I, with continuous removal of freshly formed product.

In a variant of the novel process, the product V in the reaction of II with III is reacted, without isolation from the reaction mixture, simultaneously with VI and VII, and acidic byproducts from the first reaction can be neutralized by a relatively high concentration of base VI. The procedure can be modified so that, after

carrying out the reaction of II with III, the low boiling components are removed and the resulting crude product is reacted with VI and VII, if desired in another solvent.

The novel process (reaction of V with VII) can be successfully used for the synthesis of all 6-trifluoromethyl-1,3,5-triazines I according to the definition, especially the compounds contained in Table 1. The 6-trifluoromethyl-1,3,5-triazines I are useful intermediates for crop protection agents, as disclosed in, for example, EP-A 111 442 or DE-A 39 09 146.

TABLE 1

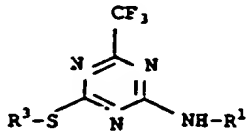


R^1	R^2
H	CH_3
H	C_2H_5
H	n-C_3H_7
H	i-C_3H_7
H	n-C_4H_9
H	i-C_4H_9
H	s-C_4H_9
H	t-C_4H_9
H	$CH_2CH=CH_2$
H	E-$CH_2CH=CHCH_3$
H	$CH_2C\equiv CH$
H	$CH_2C\equiv CCH_3$
H	Cyclopropyl
H	Cyclobutyl
H	Cyclopentyl
H	Cyclohexyl
CH_3	CH_3
CH_3	C_2H_5
CH_3	n-C_3H_7
CH_3	i-C_3H_7
CH_3	n-C_4H_9
CH_3	i-C_4H_9
CH_3	s-C_4H_9
CH_3	t-C_4H_9
CH_3	$CH_2CH=CH_2$
CH_3	E-$CH_2CH=CHCH_3$
CH_3	$CH_2C\equiv CH$
CH_3	$CH_2C\equiv CCH_3$
CH_3	Cyclopropyl

R^1	R^2
CH_3	Cyclobutyl
CH_3	Cyclopentyl
CH_3	Cyclohexyl
C_2H_5	CH_3
C_2H_5	C_2H_5
C_2H_5	$n-C_3H_7$
C_2H_5	$i-C_3H_7$
C_2H_5	$n-C_4H_9$
C_2H_5	$i-C_4H_9$
C_2H_5	$s-C_4H_9$
C_2H_5	$t-C_4H_9$
C_2H_5	$CH_2CH=CH_2$
C_2H_5	$E-CH_2CH=CHCH_3$
C_2H_5	$CH_2C\equiv CH$
C_2H_5	$CH_2C\equiv CCH_3$
C_2H_5	Cyclopropyl
C_2H_5	Cyclobutyl
C_2H_5	Cyclopentyl
C_2H_5	Cyclohexyl
$n-C_3H_7$	CH_3
$i-C_4H_9$	C_2H_5
$n-C_3H_7$	$n-C_3H_7$
$i-C_4H_9$	$i-C_3H_7$
$n-C_3H_7$	$n-C_4H_9$
$s-C_4H_9$	$i-C_4H_9$
$i-C_3H_7$	$s-C_4H_9$
$t-C_4H_9$	$t-C_4H_9$
$i-C_3H_7$	$CH_2CH=CH_2$
$t-C_4H_9$	$E-CH_2CH=CHCH_3$
$i-C_3H_7$	$CH_2C\equiv CH$
$t-C_4H_9$	$CH_2C\equiv CCH_3$
$i-C_3H_7$	Cyclopropyl
$t-C_4H_9$	Cyclobutyl
$i-C_3H_7$	Cyclopentyl
$t-C_4H_9$	Cyclohexyl

The novel process (reaction of II with III) can be successfully used for the synthesis of all 6-trifluoromethyl-1,3,5-triazines V according to the definition, especially the compounds stated in Table 2.

TABLE 2



R^1	R^3
H	CH_3
H	C_2H_5
H	n-C_3H_7
H	i-C_3H_7
H	n-C_4H_9
H	i-C_4H_9
H	s-C_4H_9
H	t-C_4H_9
H	$CH_2CH=CH_2$
H	E-$CH_2CH=CHCH_3$
H	$CH_2C\equiv CH$
H	$CH_2C\equiv CCH_3$
H	Cyclopropyl
H	Cyclobutyl
H	Cyclopentyl
H	Cyclohexyl
CH_3	CH_3
CH_3	C_2H_5
CH_3	n-C_3H_7
CH_3	i-C_3H_7
CH_3	n-C_4H_9
CH_3	i-C_4H_9
CH_3	s-C_4H_9
CH_3	t-C_4H_9
CH_3	$CH_2CH=CH_2$

R'	R''
CH_3	E-$CH_2CH=CHCH_3$
CH_3	$CH_2C\equiv CH$
CH_3	$CH_2C\equiv CCH_3$
CH_3	Cyclopropyl
CH_3	Cyclobutyl
CH_3	Cyclopentyl
CH_3	Cyclohexyl
C_2H_5	CH_3
C_2H_5	C_2H_5
C_2H_5	n-C_3H_7
C_2H_5	i-C_3H_7
C_2H_5	n-C_4H_9
C_2H_5	i-C_4H_9
C_2H_5	s-C_4H_9
C_2H_5	t-C_4H_9
C_2H_5	$CH_2CH=CH_2$
C_2H_5	E-$CH_2CH=CHCH_3$
C_2H_5	$CH_2C\equiv CH$
C_2H_5	$CH_2C\equiv CCH_3$
C_2H_5	Cyclopropyl
C_2H_5	Cyclobutyl
C_2H_5	Cyclopentyl
C_2H_5	Cyclohexyl
n-C_3H_7	CH_3
i-C_4H_9	C_2H_5
n-C_3H_7	n-C_3H_7
i-C_4H_9	i-C_3H_7
n-C_3H_7	n-C_4H_9
s-C_4H_9	i-C_4H_9
i-C_3H_7	s-C_4H_9
t-C_4H_9	t-C_4H_9
i-C_3H_7	$CH_2CH=CH_2$
t-C_4H_9	E-$CH_2CH=CHCH_3$
i-C_3H_7	$CH_2C\equiv CH$
t-C_4H_9	$CH_2C\equiv CCH_3$
i-C_3H_7	Cyclopropyl

R^2	R^3
t-C_4H_9	Cyclobutyl
i-C_3H_7	Cyclopentyl
t-C_4H_9	Cyclohexyl
H	Benzyl
CH_3	Benzyl
H	4-Methylbenzyl
H	4-Chlorbenzyl
H	3-Methoxybenzyl

EXAMPLE 1

Preparation of 2-amino-4-methylthio-6-trifluoromethyl-1,3,5-triazine (V: R^1 = H, R^3 = CH_3)

90.0 g (0.5 mol) of a 30% strength by weight solution of sodium methylate in methanol were added dropwise at 0°C to a suspension of 90.0 g (0.25 mol) of N-amidino-S-methylisothiuronium iodide (adduct of N-methyl-2-pyrrolidone) in 128.0 g (1.0 mol) of methyl trifluoroacetate, after which a homogeneous, slightly yellow solution was formed. The reaction mixture was then stirred for 5 hours at 25°C.

The volatile components were removed under reduced pressure at 40°C, the residue was stirred vigorously with 200 ml of water and the solid formed was filtered off under suction and dried under reduced pressure at 50°C.

The title compound was obtained as colorless crystals (mp. 181-183°C) in a yield of 94%.

EXAMPLE 2

Preparation of 2-amino-4-methylthio-6-trifluoromethyl-1,3,5-triazine (V: R^1 = H, R^3 = CH_3)

104.4 g (0.58 mol) of a 30% strength by weight solution of sodium methylate in methanol were added dropwise at 0°C to a suspension of 90.0 g (0.29 mol) of N-amidino-S-methylisothiuronium iodide (adduct of N-methyl-2-pyrrolidone) in 128.0 g (1.0 mol) of methyl trifluoroacetate, after which a homogeneous, slightly

yellow solution was formed. The reaction mixture was then stirred for 5 hours at 25°C. The volatile components were removed under reduced pressure at 40°C, the residue was stirred vigorously with 200 ml of water and the solid formed was filtered off under suction and dried under reduced pressure at 50°C.

The title compound, which still contained about 5% by weight of N-methyl-2-pyrrolidone, was obtained in a yield of 90%.

EXAMPLE 3

Preparation of 2-amino-4-methylthio-6-trifluoromethyl-1,3,5-triazine (V: R^1 = H, R^3 = CH_3)

23.4 g (112.2 mmol) of trifluoroacetic anhydride were added dropwise at 5-15°C to a suspension of 20.0 g (55.6 mmol) of N-amidino-S-methylisothiuronium iodide (adduct of N-methyl-2-pyrrolidone) in 100 ml of ethyl acetate and 6.2 g (61.4 mmol) of triethylamine. Stirring was carried out for 15 hours at 25°C, the mixture was diluted with 300 ml of methylene chloride and washed with 2 x 100 ml of water, the phases were separated and the organic phase was dried over Na_2SO_4. The volatile components were removed under reduced pressure at 40°C, and the oily, pale orange residue was stirred vigorously with 200 ml of water, after which crystallization occurred. The solid formed was filtered off under suction and dried under reduced pressure at 50°C.

The title compound was obtained in a yield of 80%.

EXAMPLE 4

Preparation of 2-amino-4-methylthio-6-trifluoromethyl-1,3,5-triazine (V: R^1 = H, R^3 = CH_3)

31.5 g (0.25 mol) of dimethyl sulfate were added dropwise at 30°C to a suspension of 54.0 g (0.25 mol) of N-amidinothiourea (adduct of N-methyl-2-pyrrolidone) in 250 ml of methanol. The rapidly forming homogeneous solution was stirred for 3 hours at 30°C. After the addition of 32.0 g (0.25 mol) of methyl trifluoroacetate

at 25°C, 54.0 g (0.30 mol) of a 30% strength by weight solution of sodium methylate in methanol were added dropwise at 0°C and stirring was carried out for 18 hours at 20-25°C. Neutralization was effected by adding 4 N HCl, the volatile components were removed under reduced pressure at 40°C and the residue was stirred vigorously with 200 ml of water. The product was filtered off under suction, washed with 200 ml of water and dried under reduced pressure at 40°C.

The title compound was obtained in a yield of 75%, contaminated with about 5% of the secondary product 2-amino-4-methoxy-6-trifluoromethyl-1,3,5-triazine.

EXAMPLE 5

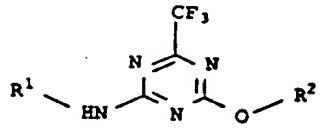
Preparation of 2-amino-4-methoxy-6-trifluoromethyl-1,3,5-triazine (I: R^1 = H, R^2 = CH_3)

40.2 g (0.22 mol) of a 30% strength by weight solution of sodium methylate in methanol were added dropwise at 0°C to a solution of 46.9 g (0.22 mol) of 2-amino-4-methylthio-6-trifluoromethyl-1,3,5-triazine and 400 ml of methanol. Stirring was carried out for 2 hours at 0°C and for 65 hours at 25°C. Neutralization was effected by adding 4 N HCl, the volatile components were removed under reduced pressure at 30°C and the residue was stirred vigorously with 100 ml of water. The product was filtered off under suction and dried under reduced pressure at 40°C.

The title compound was obtained as colorless crystals (mp. 163°C) in a yield of 85%.

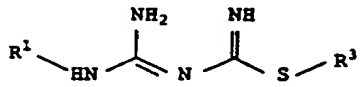
We claim:-

1. A process for the preparation of derivatives of 6-trifluoromethyl-1,3,5-triazine of the formula I



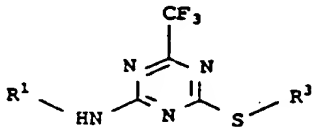
I

where R^1 is hydrogen or a C-organic radical and R^2 is a C-organic radical, wherein a salt of an N-amidino-S-alkyl-isothiourea of the formula II



II

where R^3 is a C-organic radical of 1 to 10 carbon atoms, is reacted with a halide, ester or anhydride of trifluoroacetic acid (compound III) and with a strong base (IV) to give a derivative of 6-trifluoromethyl-1,3,5-triazine of the formula V



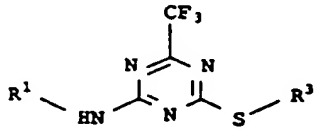
V

and the latter is converted in the presence of a base (VI) with an alcohol of the formula VII

$$R^2\text{-OH} \qquad \text{VII}$$

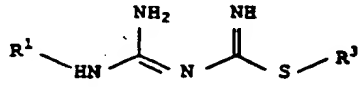
into the compound I.

2. A process for the preparation of derivatives of 6-trifluoromethyl-1,3,5-triazine of the formula V



V

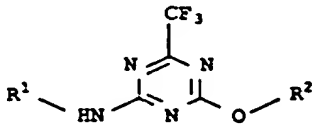
where R^1 is hydrogen or a C-organic radical and R^3 is a C-organic radical of 1 to 10 carbon atoms, wherein a salt of an N-amidino-S-alkylisothiourea of the formula II



II

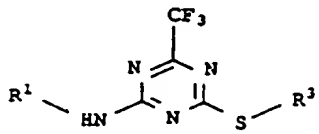
is reacted with a halide, ester or anhydride of trifluoroacetic acid (compound III) and with a strong base (IV).

3. A process for the preparation of derivatives of 6-trifluoromethyl-1,3,5-triazine of the formula I



I

where R^1 is hydrogen or a C-organic radical and R^2 is a C-organic radical, wherein a compound of the formula V



V

where R^3 is a C-organic radical of 1 to 10 carbon atoms, is converted in the presence of a base (VI) with an alcohol of the formula VII

$$R^2\text{-OH} \qquad \text{VII}$$

into the compound I.